receptor type or subtype, the potential side effects mediated through other opioid receptor types can potentially be minimized or eliminated, thus treating nausea and vomiting (see col. 1, lines 34-45).

(2) Rudd discloses naltrindole (NTI), having the same structure to inhibit emetic reflexes (vomiting) (see abstract and also page 82 (section 4.3 first paragraph). Rudd is used to show that NTI has been used to treat vomiting. Therefore, one of ordinary skill in the art would be motivated to use NTI to treat vomiting caused by a μ-opioid agonist (fentanyl).

(3) One of ordinary skill in the art would have been motivated to administer NTI to a patient wherein nausea and vomiting is caused by administration of a μ-opioid agonist (morphine) because the art teaches that NTI has been used to specifically inhibit the adverse effects of morphine.

The Applicants agree that Portoghese and Rudd disclose NTI, which is similar in structure to the Applicants' compounds in Claims 11-12, 14 and 16. However, the Applicants respectfully submit that Portoghese and Rudd, whether taken individually or collectively, do not teach inhibition of the emetic reflex with NTI.

First, the Applicants agree that Portoghese discusses selected adverse effects of morphine, wherein such effects are vomiting, depressed respiration, constipation, tolerance and dependence. However, Portoghese does not teach a method for treating nausea and vomiting at all.

Lines 34-43 of col. 1 of Portoghese state:

> If a ligand acts at a single opioid receptor type or subtype, the potential side effects mediated through other opioid receptor types can potentially be minimized or eliminated.

When this is taken in context, the Applicants respectfully submit that such disclosure essentially

states that a δ- or k-opioid agonist may be employed to treat pain without morphine (μ-opioid agonist) induced side effects. This is completely different from the subject matter of the Applicants' claims. The compounds of the Applicants' Claims 11-12, 14 and 16 are not opioid agonists, which cannot induce analgesia itself, but can treat nausea and vomiting, induced by μ-opioid agonistic analgesics (such as morphine). In other words, Portoghese teaches administration of a single active compound that is effective to treat pain, but does not produce side effects. Also, those teachings are located in the "background" discussion and have nothing to do with the subject matter of Portoghese's invention.

Second, Portoghese provides a method for treating (blocking or reducing) tolerance and dependence caused by administration of an opioid agonist (col. 2, lines 7-9), and suggests a method for inhibiting respiratory depression caused by certain opioid agonists without inhibiting their analgesic action (col. 3, lines 52-55) using NTI derivatives. At most, one of the side effects of morphine, tolerance and dependence, can be treated by an NTI derivative. Thus, the rejection speculates that one of ordinary skill in the art would have been motivated to administer the above compounds to a patient wherein the other side effect, nausea and vomiting, is caused by administration of a μ-opioid agonist.

The Applicants submit new evidence that all of the side effects induced by morphine cannot always be treated by NTI. The Applicants enclose Hepburn et al., J. Pharm. Exp. Ther., 1997, 281, pages 1350-1356 for the Examiner's convenience. In the course of the study of differential effects of NTI on morphine-induce tolerance and physical dependence, Hepburn evaluated the effect of NTI on respiratory depression induced by morphine. Hepburn confirmed the teachings of Portoghese that NTI has clinical potential for decreasing the development of tolerance. Hepburn also showed that NTI has no effect on respiratory depression induced by morphine. This is found on page 1353, right

column, second paragraph:

> NTI itself did not affect respiration, and it had no effect on the acute respiratory depressive effects of morphine.

This evidence teaches that if one of the morphine side effects, tolerance, can be treated by NTI, another side effect is not necessarily treated by the same compound. In other words, although Portoghese shows that NTI is effective for treating dependence and tolerance, it does not mean that NTI is effective for treating nausea and vomiting. Consequently, one skilled in the art would not have a reasonable expectation of success that NTI would have a positive effect on treating nausea and vomiting induced by morphine.

Rudd is further removed from the claimed subject matter than Portoghese and Rudd fails to cure the deficiencies of Portoghese with respect to teaching methods of treating nausea and vomiting caused by μ-opioid agonist.

First, it should be emphasized that μ-opioid agonists (such as morphine) show both of directly-opposed effects on emesis, namely μ-opioid agonists induce emesis (nausea, vomiting) in the low or therapeutic dose range, but on the other hand, the same compound reduces emesis (anti-emetic) in the high dose range (Barnes et al. Neuropharmacology, 1991, 30, 1073-83. Abstract). Morphine and fentanyl are both μ-opioid agonists as evidenced by Neelman and Meijer.

Rudd discloses treating emesis induced by nicotine with fentanyl (μ-opioid agonist). That has nothing to do with the Applicants' claimed subject matter which is a method for treating emesis caused by μ-opioid agonist with NTI derivative (δ -opioid antagonist). An objective of Rudd is to confirm which type of opioid receptor is involved on the fentanyl anti-emetic effect using selective opioid antagonist including NTI as a δ-opioid antagonist. The abstract and page 82 (section 4.3 first

paragraph) states:

> The anti-emetic action of fentanyl was antagonized by the opioid receptor antagonists naltrexone, naloxone, M8008 and MR 2266 but not by naloxone methylbromide, naloxone methyliodide, NTI, DIPPA or naloxonazine. This indicates an involvement of μ_2-opioid receptors within the brain mediate the anti-emetic effect of fentanyl.

Rudd shows in Table 2 (page 79) that NTI does not attenuate the effect on the emesis induced by nicotine (Nic+Nalt: sixth entry) nor on the anti-emetic effect of fentanyl (Nic+Nalt+Fent: eighth entry). In other words, Rudd teaches that NTI does not increase emesis, but does not decrease emesis.

As part of this demonstration, Rudd first administered large doses of nicotine to induce emesis. Then, fentanyl was administered to determine whether fentanyl had an anti-emetic effect. The Applicants enclose a sheet which contains the teachings of Rudd outlined in diagrammatic form. There are four entries. The first entry is the administration of nicotine. This causes emesis, as indicated by the upwardly pointing arrow. Then, fentanyl is administered. Administration of fentanyl has an anti-emetic effect, as indicated by the downward arrow next to emesis. Thus, it is demonstrated that fentanyl counteracts the emetic effect of nicotine.

The next step was the pretreatment of NTI before the administration of fentanyl. NTI did not increase emesis, but did not decrease emesis which is induced by nicotine. Furthermore, NTI did not affect anti-emetic effect of fentanyl.

Thus, the Applicants respectfully submit that Rudd does not teach administration of NTI to inhibit the emetic reflex. In sharp contrast, Rudd teaches administration of fentanyl to inhibit the emetic reflex. Administration of additional substances is performed to see if there is an effect that counteracts the anti-emetic effect of fentanyl.

The Applicants therefore respectfully submit that it is in error to take the position that Rudd

teaches NTI inhibiting the emetic reflex. Instead, the essence of Rudd is that administration of NTI has no effect on the emetic reflex subsequent to the administration of fentanyl which suppresses the emetic reflex. Again, the Applicants respectfully submit that there is no disclosure of NTI having any effect on the emetic reflex, much less inhibiting the emetic reflex.

As a result of this failure on the part of Rudd, utilizing Rudd in conjunction with Portoghese fails to provide teachings that would lead one skilled in the art to the claimed subject matter. This is because Portoghese does not disclose the administration of NTI to reduce emesis caused by μ-opioid agonist compounds, as claimed. Instead, Portoghese discloses to treat pain such that there is reduced tolerance and dependence. There is no mention of administering NTI in conjunction with reducing emesis, much less administering NTI to inhibit emesis caused by a μ-opioid agonist compound.

Also, there is no incentive to combine the teachings of Rudd with Portoghese because Portoghese teaches that NTI has no emetic effect. Instead, Rudd teaches that NTI has no effect on emesis. Therefore, one skilled in the art would not have a reasonable expectation that administration of NTI would have an anti-emetic effect on emesis caused by a μ-opioid agonist compound. In fact, the Applicants respectfully submit that one skilled in the art would have a reasonable expectation of failure that NTI would have the desired anti-emetic effect based on the teachings of Rudd. Thus, even if those teachings are combined, it would not lead one skilled in the art to the subject matter of the Applicants' claims.

As noted above, Portoghese discloses administration of NTI derivatives only for the treatment on the specific type of side effect, tolerance and dependence. The Applicants respectfully submit that the Applicants have found another type of and unpredictable indication of NTI derivatives. The teachings of Rudd would lead one skilled in the art to have the reasonable expectation that the use of NTI would have no effect on emesis induced by nicotine nor on anti-

emesis caused by fentanyl. As such, one skilled in the art would not make that combination and would not use NTI to treat emesis caused by μ-opioid agonists. Thus, the hypothetical combination as set forth in the rejection is inapplicable to Claims 11-12, 14 and 16. Withdrawal of the rejection is respectfully requested.

Neeleman discloses that morphine is a μ-opioid receptor agonist and Meijer discloses that fentanyl is also a μ-opioid agonist. This is confirmed in the rejection and the Applicants have no disagreement with that point. However, it is irrelevant. Hypothetically combining that teaching from Neeleman with Rudd and Portoghese does not cure the deficiency of those two references. Therefore, the combination of Neeleman with Portoghese and Rudd still fails to result in what the Applicants claim.

The rejection specifically states that:

> One of ordinary skill in the art would have been motivated to administer the above compounds to a patient wherein the nausea and vomiting is caused by the administration of a mμ-opiod agonist (morphine) because the art teaches that naltrindole has been used to specifically inhibit adverse effects of morphine. One of ordinary skill in the art would have been motivated to use the drug, to inhibit vomiting. Therefore one of ordinary skill in the art would have been motivated to administer the drug since the compound as taught has the property of reducing vomiting/nausea as a whole, and would expect the drug to work since the action of is blocking of the stimulation of the emesis zone as it was found to be a member of the morphinan that prevents emetics.

The Applicants respectfully submit that it would have been anything but obvious to make the combination. As noted above, Portoghese discloses the administration of NTI with a μ-opioid agonist compound to treat pain and reduce dependence and tolerance.

However, this does not mean that one skilled in the art would employ NTI as a emetic inhibitor based on the teachings of Rudd. The teachings of Rudd would lead one skilled in the art to

have the reasonable expectation that the use of NTI would have no effect on emesis. As such, one skilled in the art would not make that combination and would not use NTI to treat emesis caused by other μ-opioid agonist compounds.

In light of the fact that Rudd teaches that NTI has no emetic effect on fentanyl, one skilled in the art would have no reasonable expectation that utilization of NTI as anti-emetics against μ-opioid agonist compound-induced emesis. Thus, the hypothetical combination as set forth in the rejection is inapplicable to Claims 11 – 12, 14 and 16. Withdrawal of the rejection is respectfully requested.

In light of the foregoing, the Applicants respectfully submit that the entire Application is now in condition for allowance, which is respectfully requested.

Respectfully submitted,

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Outline of Teachings of Rudd